ORIGINAL RESEARCH

Mortality and Disability According to Baseline Blood Pressure in Acute Ischemic Stroke Patients Treated by Thrombectomy: A Collaborative Pooled Analysis

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***Background*—**High blood pressure (BP) is associated with worse clinical outcomes in the setting of acute ischemic stroke, but the optimal blood pressure target is still a matter of debate. We aimed to study the association between baseline BP and mortality in acute ischemic stroke patients treated by mechanical thrombectomy.

***Methods and Results*—**A total of 1332 acute ischemic stroke patients treated by mechanical thrombectomy were enrolled (from January 2012 to June 2016) in the ETIS (Endovascular Treatment in Ischemic Stroke) registry. Linear and polynomial logistic regression models were used to assess the association between BP and mortality and functional outcome at 90 days. Highest mortality was found at lower and higher baseline systolic blood pressure (SBP) values following a J- or U-shaped relationship, with a nadir at 157 mm Hg (95% confidence interval 143-170). When SBP values were categorized in 10–mm Hg increments, the odds ratio for all-cause mortality was 3.78 (95% confidence interval 1.50-9.55) for SBP<110 mm Hg and 1.81 (95% confidence interval 1.01-3.36) for SBP≥180 mm Hg using SBP≥150 to 160 mm Hg as reference. The rate of favorable outcome was the highest at low SBP values and lowest at high SBP values, with a nonlinear relationship; in unplanned exploratory analysis, an optimal threshold SBP≥177 mm Hg was found to predict unfavorable outcome (adjusted odds ratio 0.47; 95% confidence interval 0.31-0.70).

***Conclusion*—**In acute ischemic stroke patients treated by mechanical thrombectomy, baseline SBP is associated with all-cause mortality and favorable outcome. In contrast to mortality, favorable outcome rate was the highest at low SBP values and lowest at high SBP values. Further studies are warranted to confirm these findings. **(*J Am Heart Assoc*. 2017;6:e006484. DOI: 10.1161/JAHA.117.006484.)**

Key Words: blood pressure • ischemic • stroke • stroke management • thrombectomy

Mechanical thrombectomy (MT) in addition to intravenous (IV) tPA (tissue-type plasminogen activator) is now the standard of care for acute ischemic stroke (AIS) patients with large-vessel occlusion (LVO) of the anterior circulation.[1] With the implementation of MT in AIS care, specific issues need to be addressed. The target for blood pressure (BP)

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Accompanying Tables S1 through S6 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/6/10/e006484/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Baseline blood pressure is associated with mortality and disability in a cohort of acute ischemic stroke patients with large vessel occlusion treated by mechanical thrombectomy.

What Are the Clinical Implications?

- Initial blood pressure management of acute ischemic stroke patients with large vessel occlusion may impact mechanical thrombectomy. Further studies are needed to confirm blood pressure targets to be achieved in the setting of acute ischemic stroke.

before MT is one of them and remains a source of controversy. Hypertension is frequently encountered in up to 50% of AIS patients[2,3] and is known to be associated with worsened functional outcome and death.[4,5] In a systematic review including AIS and hemorrhagic stroke patients, a baseline SBP between 150 and 200 mm Hg was correlated with mortality, but with limited evidences of a potential threshold effect.[2] A trend of SBP increase was linked with subsequent death or dependency. Based on findings from the SITS (Safe Implementation of Thrombolysis in Stroke) registry, that included IV tPA-treated patients, SBP was associated with worse outcomes following a U-shaped relationship with mortality and independence.[6] In the SITS registry, patients with SBP between 141 and 150 mm Hg had the most favorable outcome. However, the status of the intracranial artery (ie, recanalized or not) in these studies was not known, and we may suppose a differential impact of BP values in the setting of persistent arterial occlusion (eg, worsening of hypoperfusion in case of BP drop) or recanalization (eg, increase in reperfusion lesions for high BP values). In the recent randomized clinical trials that have proven the efficacy of MT,[7–12] BP monitoring was not analyzed systematically. Despite the limited evidence, the current guidelines for AIS patients undergoing MT recommend that BP should be kept below 180/110 mm Hg.[13] Patients treated by MT are a homogeneous AIS population with LVO, potentially with different BP profiles from the overall AIS population including those without LVO. The impact of BP on mortality in this specific population remains to be assessed. Our aim was to study the association between BP and mortality in a cohort of AIS patients with LVO and eligible for MT from the ETIS (Endovascular Treatment in Ischemic Stroke) registry.

Methods

The ETIS registry is a French multicenter prospective collected database from 3 comprehensive stroke centers (Rothschild Foundation, Foch Hospital, and Pierre Wertheimer Hospital),[14] including AIS patients with LVO and treated with MT, between January 2012 and June 2016. Criteria for inclusion were AIS proven on cerebral imaging (magnetic resonance imaging or computed tomography) and a proven LVO on the anterior and posterior circulation on baseline magnetic resonance angiography or computed tomography angiography; patients were eligible if they were treatable by MT within 8 hours of stroke onset for anterior circulation and 12 hours for posterior circulation. All patients had computed tomography or magnetic resonance imaging 24 hours after treatment onset to assess hemorrhagic complications. Admission BP was defined by the BP measured at the first contact with the stroke team.

Exclusion criteria included the absence of LVO on the baseline digital subtraction angiography; missing detailed baseline data concerning history of hypertension and value of BP at baseline; absence of brain imaging at 24 hours; and the absence of functional outcome assessment (modified Rankin Scale [mRS]) at 3 months. Pretreatment and day-1 National Institutes of Health Stroke Scale (NIHSS) were assessed by stroke neurologists and functional outcome at 3 months by the mRS score either face-to-face or by phone interviews (median follow-up, 98 days, interquartile range, 86-113) by observers blinded to the clinical events.

Clinical Outcome Definitions

The primary study outcome was the percentage of all-cause mortality. Secondary outcomes included good outcome, defined as a mRS score of 0-2 at 3 months, and symptomatic intracranial hemorrhage (sICH). Intracranial hemorrhage (ICH) was classified according to the European Cooperative Acute Stroke Study criteria.[15] Symptomatic ICH was defined as an increase of 4 points or more of NIHSS within 24 hours attributable to ICH.

A local ethics committee and the French Data Protection Agency approved the use of patient data for this research protocol. In accordance with the French legislation, informed consent was not needed from patients because this study used analysis of only anonymized data collected prospectively as a part of routine clinical care.

Statistical Analysis

Quantitative variables are expressed as means±standard deviation in cases of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Primary analysis was conducted among 1042 patients for whom baseline BP and 90-day mRS were available. To assess the selection bias due to these missing data, patient

characteristics were described in terms of the included and nonincluded patients, and the magnitudes of the between-group differences were assessed by calculating the absolute standardized differences; an absolute standardized difference <0.2 was interpreted as a small difference.[16] Patient characteristics were compared according to the clinical outcomes (90-day all-cause mortality, favorable outcome, and sICH) using the chi-squared test or Fisher exact test for categorical variables and Student t test (or Mann-Whitney U-test in cases of nonnormal distribution) for quantitative variables as appropriate. To describe the association of baseline BP levels with each clinical outcome, BP values were categorized in 10–mm Hg increments from 110 to 180 mm Hg for SBP and from 60 to 110 mm Hg for diastolic BP (DBP).

Because we had hypothesized a J- or U-shaped association (with low BP level as a negative factor,[17] we used both linear and polynomial logistic regression models to assess the association of BP with each clinical outcome. Polynomial logistic regression models were estimated by including linear and quadratic BP terms (a second-order polynomial regression model), and overall BP associations were examined on the basis of a likelihood ratio test. We also used a graphical approach using nonparametric smoothing techniques to establish whether other transformations were needed to analyze the association between baseline BP and each clinical outcome[18]; a smooth curve was obtained by fitting a generalized additive model (binomial distribution with a logit link function) with a cubic smoothing spline term. We observed a threshold dose relationship between baseline SBP and favorable outcome, and so we determined the optimal cutoff value using the receiver operating characteristic curve analysis by maximizing the Youden index. We therefore fitted a logistic regression model including baseline SBP as a binary variable according to this cutoff value. For each outcome, we used the Akaike information criterion (AIC) to compare and determine the best-fitted model.[19] All logistic regression models were further stratified by center and adjusted for the following prespecified potential confounding factors: age, sex, history of hypertension and diabetes mellitus, baseline NIHSS, and prior use of thrombolysis. Because a J- or U-shaped relationship between baseline SBP and 90-day all-cause mortality was established, we determined from the regression coefficients of the polynomial multivariate logistic regression model the SBP value at which the predicted all-cause mortality was the lowest (the nadir value), 95% confidence interval (CI) of the nadir value was calculated using a bootstrap method (2000 resamplings). To illustrate this J- or U-shaped relationship, we calculated the adjusted odds ratio (OR) for low SBP values (<110 mm Hg) and for high SPB values (≥180 mm Hg) using the SBP category, which included the nadir value (≥150-160 mm Hg) as reference.

Heterogeneity of the association of baseline BP on each clinical outcome according to the recanalization status (TICI [Thrombolysis in Cerebral Infarction] 2b/3 versus TICI 0-1/2a) was investigated by including the corresponding interaction terms into the adjusted logistic regression models. Finally, we performed a sensitivity analysis after handling missing data on baseline BP and outcomes by multiple imputation using a regression switching approach (chained equations with m=10 imputations obtained using the R statistical software version 3.03; R Foundation, Vienna, Austria).[20] The imputation procedure was performed under missing at random assumption using all patient's characteristics, 90-day mRS and sICH with predictive mean matching method for quantitative variables and logistic regression model (binary, ordinal, or multinomial) for categorical variables. Regression estimates obtained in the different imputed data sets were combined using the Rubin rules.[21]

Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results

During the study period, a total of 1332 AIS patients with documented arterial occlusion were consecutively treated in the 3 participating centers by an endovascular approach (IV tPA and/or MT±prior use of IV tPA). Patient characteristics, revascularization, and clinical outcomes are reported by participating centers in Table S1. Of these, 290 patients were excluded from the primary analysis due to the absence of follow-up at 90 days (n=126) or missing data on baseline BP values (n=196). Characteristics of included and nonincluded patients in primary analysis are reported in Table S2; there were no major differences except a greater onset to groin-puncture time in excluded patients (standardized difference=21%).

Of the 1042 analyzed patients, successful reperfusion occurred in 74.5% (n=389 with TICI 2b, n=378 with TICI 3), all-cause mortality at 90 days in 21.1% (n=220), favorable outcome (90-day mRS 0-2) in 47.7% (n=497), and sICH in 9.6% (n=98). The median follow-up was 98 days (interquartile range 86-113). Patient characteristics at baseline are reported overall and according to primary outcome (90-day all-cause mortality) in Table 1. In comparison to patients alive at 90 days, patients who died were older, more frequently had hypertension, diabetes mellitus, and anticoagulant history, were admitted with a more severe AIS (assessed by NIHSS and Diffusion Weighted Imaging - Alberta Stroke Program Early Computed Tomography Scores (DWI-ASPECTS)), less often had an isolated MCA occlusion, more frequently received IV tPA before MT, and were more often treated under general anesthesia. Patient characteristics according to

Table 1. Patient's Characteristics Overall and According to All-Cause Mortality at 90 Days

		All-Cause Mortality		
	Overall	No	Yes	*P* Value
Number of patients	1042	822	220	
Age, y, mean±SD	67.6±15.0	66.1±15.1	73.4±13.1	<0.001
Men	538 (51.6)	421 (51.2)	117 (53.2)	0.60
Medical history				
Hypertension	587 (56.3)	439 (53.4)	148 (67.3)	<0.001
Diabetes mellitus	163 (15.7)	106 (12.9)	57 (25.9)	<0.001
Hypercholesterolemia	304 (29.2)	231 (28.2)	73 (33.2)	0.15
Current smoking	223 (22.8)	188 (24.1)	35 (17.5)	0.047
Antithrombotic therapy	399 (38.6)	298 (36.5)	101 (46.1)	0.010
Antiplatelet	258 (24.9)	195 (23.9)	63 (28.8)	0.28
Anticoagulant	181 (17.5)	127 (15.6)	54 (24.7)	0.002
NIHSS score, median (IQR)	16 (11-21)	15 (10-19)	20 (16-23)	<0.001
DWI-ASPECTS, median (IQR)	7 (6-9)	8 (6-9)	7 (4-8)	<0.001
Baseline SBP, mm Hg, mean±SD	149±25	148±25	151±28	0.15
Baseline DBP, mm Hg, mean±SD	81±17	81±16	83±19	0.039
Site of occlusion				
Isolated MCA	630 (60.5)	521 (63.4)	109 (49.6)	<0.001
ICA with or without tandem MCA	307 (29.5)	226 (27.5)	81 (36.8)	
Vertebrobasilar	105 (10.1)	75 (9.1)	30 (13.6)	
Previous use of IV thrombolysis	652 (62.6)	531 (64.6)	121 (55.0)	0.002
Onset to groin puncture, min, median (IQR)	242 (190-295)	241 (190-283)	245 (193-300)	0.66

Values are number (percentage) unless otherwise as indicated. ASPECTS indicates Alberta Stroke Program Early Computed Tomography score; DBP, diastolic blood pressure; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

presence or absence of favorable outcome and sICH are available in Tables S3 and S4.

Baseline Blood Pressure and 90-Day All-Cause Mortality

The highest all-cause mortality incidence was found at lower and higher baseline SBP values (Figure S1A). In logistic regression analysis a J- or U-shaped relationship with SBP was observed with models including linear and quadratic terms (Table 2), which was confirmed by the nonparametric smoothing spline method (Figure 1A). After adjustment for prespecified confounding factors (ie, center, age, sex, history of hypertension and diabetes mellitus, baseline NIHSS, and prior use of thrombolysis), the nonlinear relationship was more pronounced. From this multivariate polynomial logistic regression model, we identified a SBP value of 157 mm Hg (95% CI 143-170), which predicted the lowest all-cause death rate. When BP values were categorized in 10–mm Hg increments, the odds for all-cause mortality increased by 3.78 (95% CI 1.50-9.55)-fold in SBP<110 mm Hg and by 1.81 (95% CI 1.01-3.36)-fold in SBP≥180 mm Hg using SBP≥150 to 160 mm Hg as reference.

Regarding baseline DBP values, a linear association was found in univariate and multivariate analyses (Figure 1B, Table 2, and Figure S1B), with an adjusted OR per 10 mm Hg of 1.11 (95% CI 1.01-1.22). Similar results were found in sensitivity analysis (Table 2). No significant heterogeneity in the relationship between baseline BP and 90-day all-cause mortality according to successful recanalization was found in linear (P>0.76) or nonlinear (P>0.64) logistic regression models.

Baseline Blood Pressure and Favorable Outcome

In contrast to mortality, the rate of favorable outcome was highest at low SBP values and lowest at high SBP values (Figure S2A). In a linear logistic regression model, baseline SBP values were significantly associated with a decreased

Table 2. Linear and Polynomial Logistic Regression Analysis of the Association of 90-Day All-Cause Mortality With Baseline Systolic and Diastolic Blood Pressure Values

Blood Pressure	Model	β (95% CI)	*P* Value	Adjusted β (95% CI)*	*P* Value*	Adjusted β (95% CI)*†	*P* Value*†
Systolic	Model 1						
	Linear term	0.0428 (−0.0149 to 0.1000)	0.15	0.0031 (−0.0637 to 0.0700)	0.93	0.0063 (−0.0573 to 0.0699)	0.85
		AIC=1076.11		AIC=899.43			
	Model 2						
	Linear term	−0.4685 (−0.9394 to 0.0024)	0.051	−0.9282 (−1.4551 to −0.4012)	<0.001	−0.7493 (−1.2406 to −0.2579)	0.003
	Quadratic term	0.0162 (0.0013 to 0.0311)	0.032	0.0296 (0.0130 to 0.0461)	<0.001	0.0241 (0.0087 to 0.0395)	0.002
	Overall effect	AIC=1073.55	0.036‡	AIC=890.09	0.003‡		0.011‡
Diastolic	Model 1						
	Linear term	0.1000 (0.0128 to 0.1871)	0.0246	0.1059 (0.0119 to 0.1999)	0.027	0.1092 (0.0230 to 0.1954)	0.013
		AIC=1073.23		AIC=894.61			
	Model 2						
	Linear term	−0.1370 (−0.6018 to 0.3277)	0.56	−0.0563 (−0.5372 to 0.4246)	0.82	−0.0272 (−0.4845 to 0.4300)	0.91
	Quadratic term	0.0131 (−0.0122 to 0.0383)	0.31	0.0089 (−0.0171 to 0.0350)	0.50	0.0075 (−0.0173 to 0.0323)	0.55
	Overall effect	AIC=1074.19	0.049‡	AIC=896.16	0.071‡		0.040‡

β indicates regression coefficient associated with baseline BP (expressed for each increase of 10 mm Hg) calculated from logistic regression models. Model 1 indicates a linear logistic regression analysis, and Model 2 indicates a nonlinear (second-order polynomial) logistic regression analysis. AIC indicates Akaike Information Criterion; BP, blood pressure; CI, confidence intervals; NIHSS, National Institutes of Health Stroke Scale.

*Logistic regression model stratified by center and adjusted for age, sex, history of hypertension and diabetes mellitus, baseline NIHSS, and prior use of thrombolysis.

†Calculated after handling missing data on outcome, BP, and other covariates using multiple imputation procedure (m=10).

‡Overall BP effect calculated using a likelihood ratio test comparing the models with and without linear and quadratic BP terms.

favorable outcome rate (OR per 10–mm Hg increase, 0.89; 95% CI 0.84-0.94). Compared to linear logistic regression model, the fit (assessed using the AIC) of the logistic regression model was not improved by using a second-order polynomial function (Table S5). When a nonparametric smoothing spline method was used, the shape of the relationship appeared nonlinear, with a curve presenting an inflection point around 180 mm Hg (Figure 2A). Using receiver operating characteristic curve analysis, we identified a value of 177 mm Hg as the optimal cutoff value for discriminating favorable from poor outcome. With this cutoff value, the fit of the logistic regression model (AIC=1424.26) was similar to those including baseline SBP as continuous variable (AIC=1424.25), with an OR of favorable outcome of 0.44 (95% CI, 0.31-0.62, $P<0.001$) for SBP≥177 mm Hg. This OR was not modified after adjustment for prespecified confounding factors (0.47; 95% CI 0.31-0.70; AIC=1147.60) or in sensitivity analysis handling missing data by multiple imputation (adjusted OR 0.51; 95% CI 0.35-0.76). We found no difference in the association of high SBP values between patients with and without successful recanalization (*P* for heterogeneity=0.78).

In univariate analysis an inverted J- or U-curve was observed for the relationship between baseline DBP and favorable outcome (Figures 2B and S2B). However, in multivariate analysis, DBP was not significantly associated with favorable outcome in either linear ($P=0.11$) or polynomial ($P=0.10$) logistic regression models (Table S5). We also found no significant heterogeneity in the relationship between baseline DBP and favorable outcome according to successful recanalization (*P* for heterogeneity >0.44 in linear and polynomial models). In addition, sICH incidence was not significantly related to baseline SBP and DBP in either linear or nonlinear logistic regression models (Figure 3, Table S6 and Figure S3).

Discussion

In the present analysis of AIS patients with LVO treated by MT included in the ETIS registry, BP was associated with

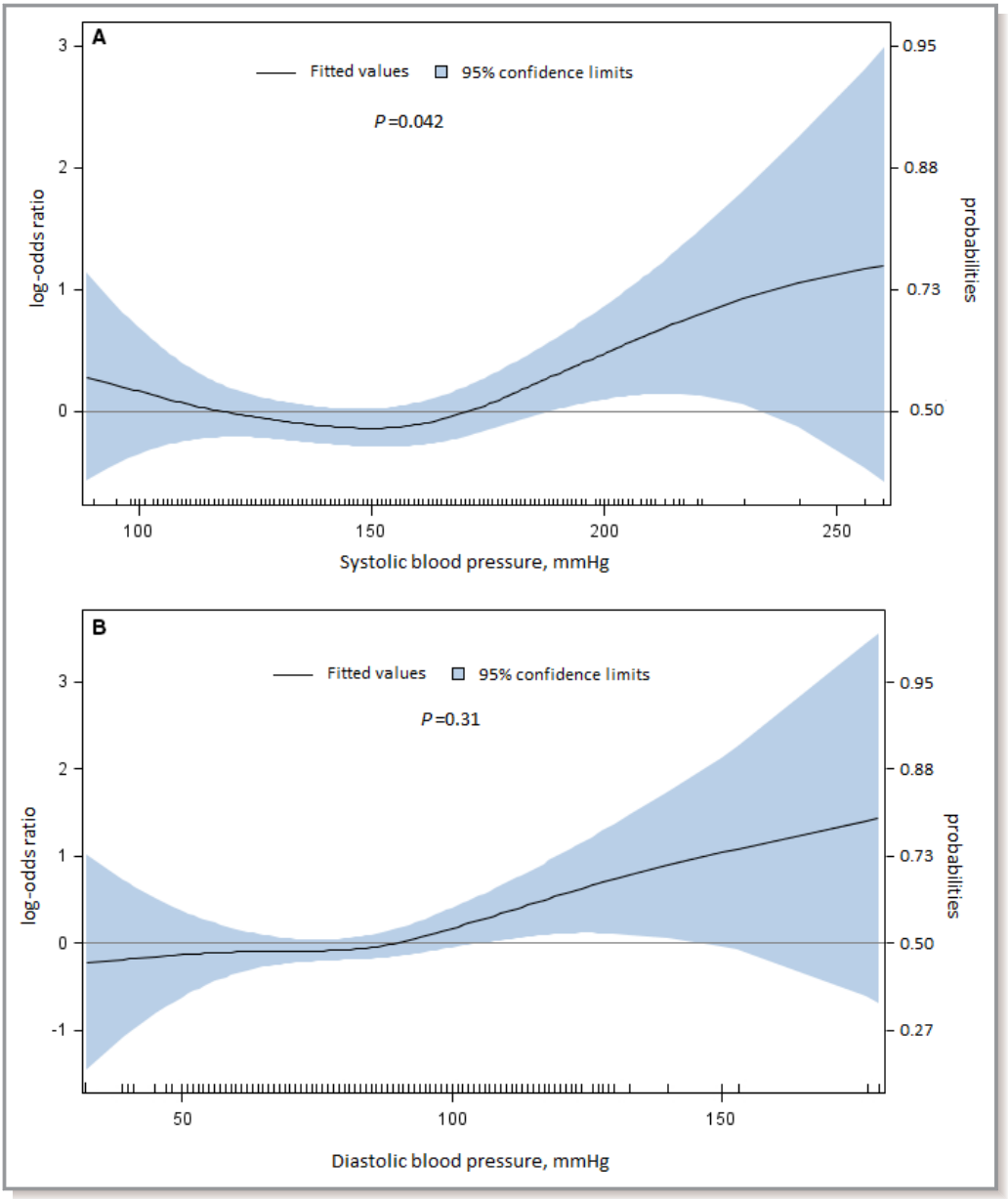

Figure 1. Relationship between 90-day all-cause mortality and systolic blood pressure (A) and diastolic blood pressure (B) at baseline. *P*-values of the likelihood ratio test comparing the full model (including both nonparametric component and linear terms) to the model including a linear term only.

mortality. For SBP, the relationship with mortality was J-shaped, involving a nadir at 157 mm Hg, whereas it remained linear for DBP. Interestingly, the relationship with SBP and favorable outcome was different, with increased favorable outcomes for low SBP and reduced ones for high SBP values including a threshold at 180 mm Hg.

The findings on mortality parallel those observed in patients with acute coronary syndromes including a J- or U-curve relationship with vascular death or all-cause mortality.[22] The value for the nadir at 156/84 mm Hg is higher than what is usually reported in the coronary artery disease population.[23] Reasons for this difference may be related to the acute process or the higher prevalence of hypertension in AIS patients. Patients with chronic hypertension are more prone to hypertensive response, with brain autoregulation shifted to higher BP levels, potentially with brain parenchyma more vulnerable to fast and intensive BP reduction.[4,5] The present data also show a discrepancy in the relationship between BP and either mortality or disability. A J-shaped curve is observed for mortality, whereas a linear curve with a threshold at 180 mm Hg is documented for functional outcome. These data suggest potential differences in the pathophysiological etiology for clinical prognosis. Mortality may be driven by cardiovascular events explaining the

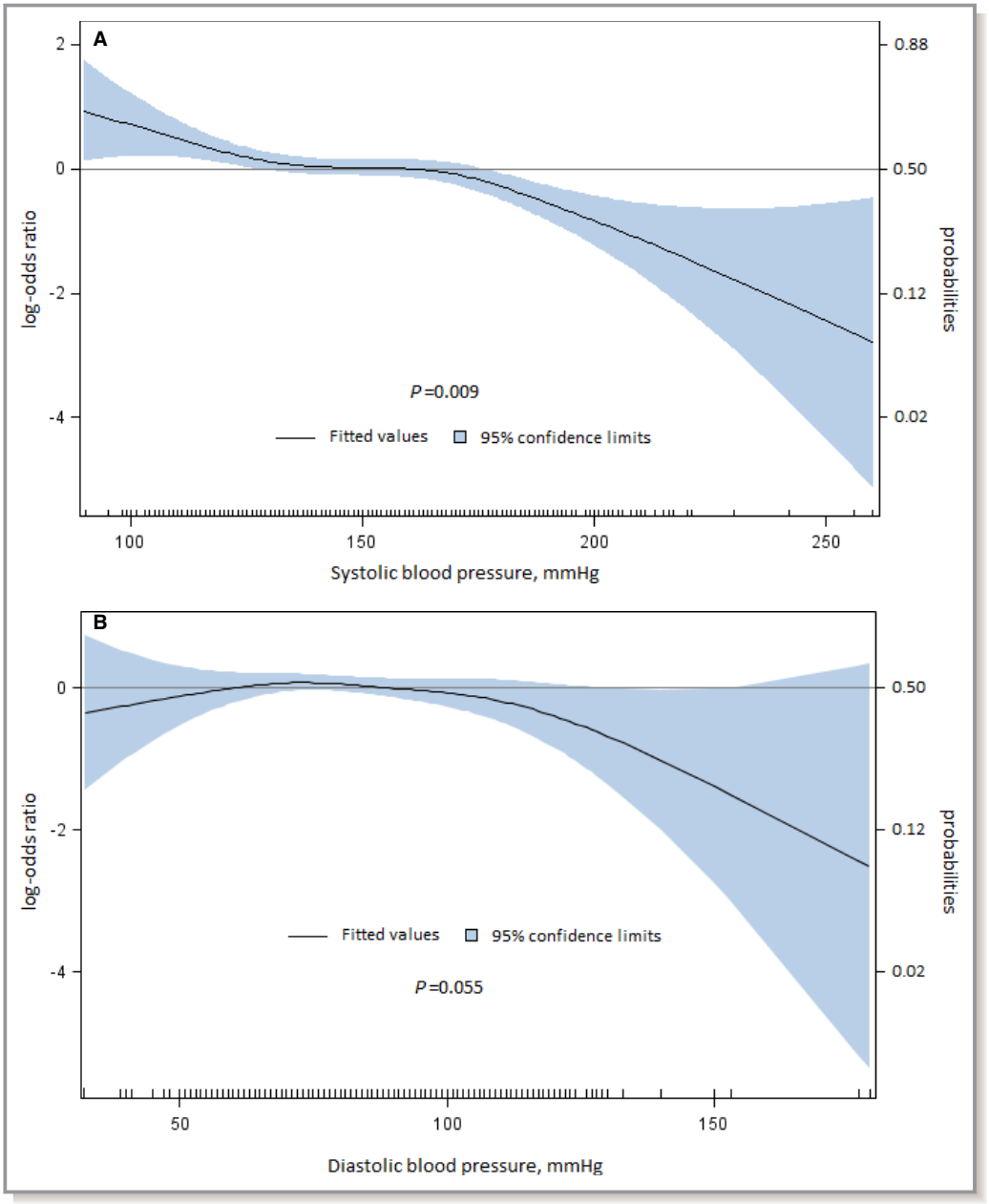

Figure 2. Relationship between favorable outcome and systolic blood pressure (A) and diastolic blood pressure (B) at baseline. *P*-values of the likelihood ratio test comparing the full model (including both nonparametric component and linear terms) to the model including a linear term only.

similarity of the J-shaped relationship described in the acute coronary syndrome population. More specifically, low BP may be involved in insufficient coronary blood supply, explaining an increased mortality related to cardiovascular events.[24] One could expect an impact on cerebral blood flow regulation, with a negative effect of low BP. Significant falls in BP could reduce cerebral blood flow and contribute to brain infarction extension. The absence of deleterious effect of low SBP on functional outcome suggests a prominent role of higher SBP values on reperfusion lesions. Still, we cannot exclude a more severe scenario in which low SBP will contribute to modify the clinical course of large brain ischemia into fatal strokes. Baseline high SBP in the setting of LVO could also be considered as an indirect marker of intracranial hemodynamic, underlying the need for good intracranial collaterals as it was described in tPA-treated patients.[25] The duality of the relationship between BP and mortality on one side and functional outcome on the other side remains unclear and complex. Additional processes may be involved, such as the stunned brain, characterized by a prolonged depression of brain functions after the recanalization of severe LVO.[26]

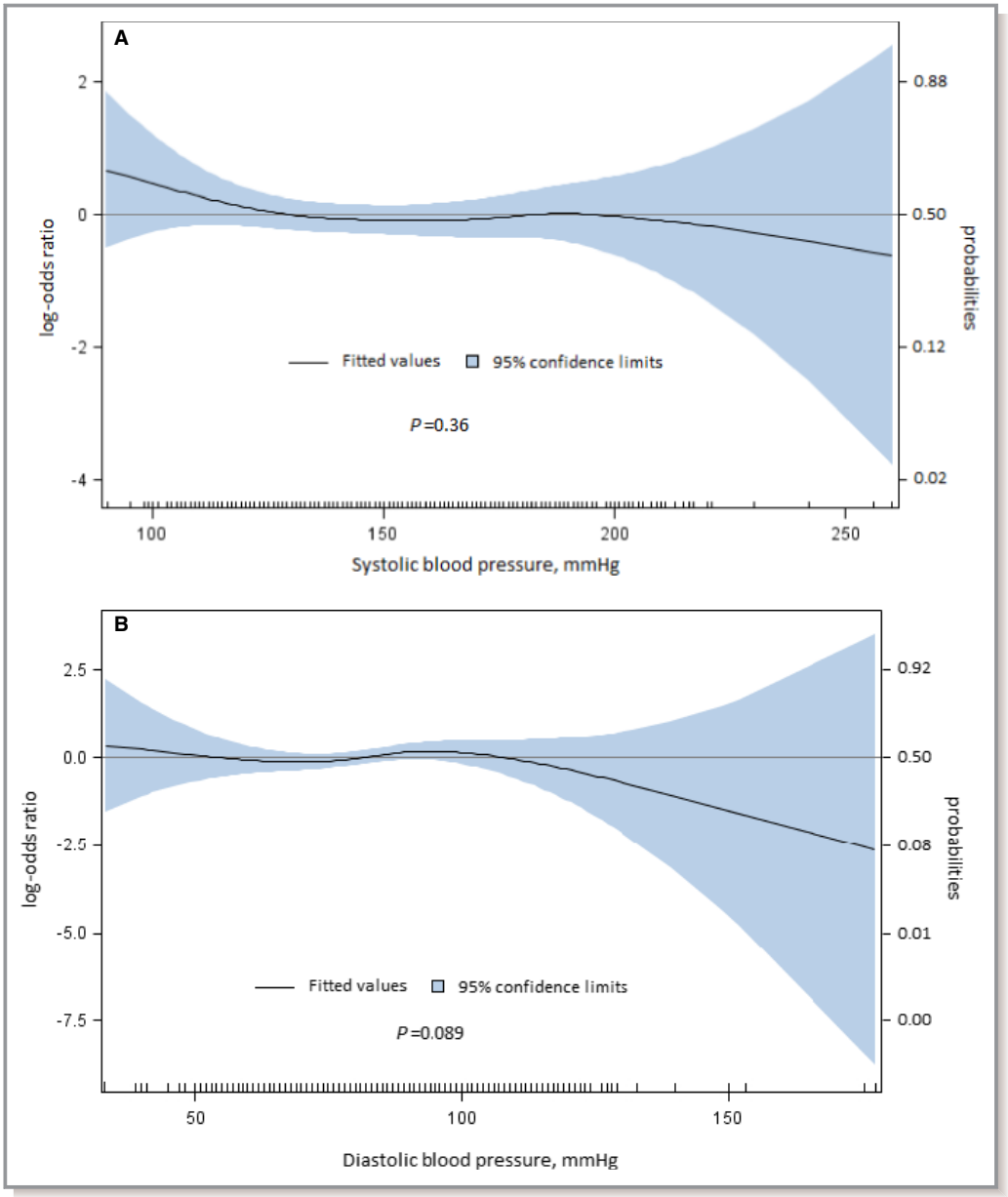

Figure 3. Relationship between symptomatic intracerebral hemorrhage and systolic blood pressure (A) and diastolic blood pressure (B) at baseline. *P*-values of the likelihood ratio test comparing the full model (including both nonparametric component and linear terms) to the model including a linear term only.

In the SITS registry the relationship between BP and functional outcome (including mortality) followed a U-shaped curve[6] with patients experiencing the best favorable outcomes when SBP was between 141 to 150 mm Hg. If the difference between mortality and disability was not reported in these earlier studies, it may be the result of the homogeneity of our studied population including AIS patients with LVO. The more linear association of baseline systolic BP with 90-day favorable outcome, observed in the present study, may be due to thrombectomy, perhaps by successful recanalization, or the obvious difference in case mix, because in this cohort all patients have LVO. Previous studies[27-29] included a more heterogeneous population with patients (without systematic imaging of intracranial vessels) treated with IV tPA, whereas the present study focuses on AIS patients with LVO documented by conventional angiography. For patients who do not undergo MT, the recanalization status is assessed by color-coded Doppler or computed tomographic angiography. This fact induces heterogeneity for arterial status assessment and monitoring (ie, recanalization grading and exact time of recanalization), which is certainly a limit to evaluating the impact of BP on prognosis because the efficacy

of the reperfusion therapy (either IV tPA and/or MT) is not precisely documented. Deleterious effects of BP values may vary based on the presence or absence of arterial occlusion. However, we did not observe a difference in the impact of BP values in patients experiencing reperfusion. The limited number of patients with persistent occlusion (74.5% rate of reperfusion in this population) and the absence of data on BP after reperfusion or persistent occlusion limit the interpretation of this finding.

Current guidelines recommend that the BP target in AIS patients should be maintained below 220/120 mm Hg and below 185/110 mm Hg in patients eligible for IV tPA.[30–32] The latest guidelines for patients who qualify for MT target 180/110 mm Hg,[13] but evidence supporting these guidelines is limited and, for some of them, based on extrapolation from data in acute myocardial infarction.[33,34] Our results suggesting a SBP threshold of 180 mm Hg for favorable outcome reinforces the current guidelines. Ongoing trials (eg, ENCHANTED [Enhanced Control of Hypertension and Thrombolysis in Stroke Study][35]) will test whether intensive BP lowering with a SBP target of 140 mm Hg improves outcomes with a lower intracranial hemorrhagic risk. We know from the SITS-MOST study (10 812 patients included) that high baseline SBP is associated with an increased sICH risk.[36] Among IV tPA-treated patients presenting with a SBP>180 mm Hg, the sICH risk reaches 12.4%, a number significantly over those reported in the European Cooperative Acute Stroke Study or SITS-MOST, respectively 5.3% and 1.9%. In our study the threshold of 180 mm Hg for SBP was associated with a worse functional outcome but not with sICH hemorrhage. The small numbers of sICH events in the present study may account for the absence of detected effect of SBP. Additional limits of the study include the characteristics of the population, which comes from a registry of AIS patients with LVO of anterior and posterior circulation. These findings cannot be extrapolated to other populations. The effect of BP may be different considering younger or older populations or a higher prevalence of patients with unstable coronary disease. In addition, we could not exclude bias in estimates from complete-cases analysis due to missing data on outcome and BP values. Indeed, we observed some large differences in regression estimates for favorable outcome between primary analysis (complete case) and sensitivity analysis (multiple imputation). These differences could be explained by a greater time to groin puncture from symptom onset and a lower isolated MCA occlusion rate in missing cases compared to nonmissing cases, underlying a not completely at random missing data mechanism. Finally, this analysis focuses on one time point of a patient's management, and BP levels within the first few hours and over 24 hours would have been informative. It underestimates the role of other parameters such as BP variability or antihypertensive agents received during stroke management or socioeconomic status that may have had an impact on prognosis. Although we did not adjust for each antihypertensive agent, the results were adjusted for presence of antihypertensive therapy. Further studies including BP measures during and after MT are needed to clarify the impact of BP variability and BP treatment on mortality, disability, and hemorrhagic transformation.[37]

In AIS patients eligible for MT, a J-shaped relationship between BP and mortality exists. This relationship differs for favorable clinical outcome, where SBP has a deleterious effect for values above 180 mm Hg. Additional randomized evidence is needed to clarify BP management in AIS patients planned for thrombectomy.

Appendix

ETIS (Endovascular Treatment in Ischemic Stroke) Research Investigators

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Patient's characteristic and outcomes in the 3 participating centers

	Center n°1 (n=876)		Center n°2 (n=295)		Center n°3 (n=161)	
	N	Values	N	Values	N	Values
Age, y mean ± SD	876	66.9 ± 15.0	295	68.0 ± 14.8	161	67.8 ± 16.2
Men	875	463 (52.9)		151 (51.2)		86 (53.4)
Medical history						
Hypertension	875	501 (57.3)	295	157 (53.2)	83	56 (51.6)
Diabetes	873	167 (19.1)	294	25 (8.3)	161	23 (14.3)
Hypercholesterolemia	873	239 (27.4)	293	101 (34.5)	161	42 (26.1)
Current smoking	873	164 (18.8)	233	88 (33.8)	160	28 (17.5)
Antithrombotic therapy	872	322 (36.9)	294	127 (43.2)	135	53 (39.3)
Antiplatelet		*221 (25.3)*		*77 (26.3)*		*37 (27.4)*
Anticoagulant		*143 (16.4)*		*58 (19.8)*		*18 (13.3)*
NIHSS score, median (IQR)	869	16 [11-20]	292	16 [10-21]	119	17 [12-22]
DWI-ASPECTS, median (IQR)	766	7 [6-9]	283	7 [6-8]	159	8 [6-8]
Baseline SBP, mmHg, mean±SD	712	149 ± 25	294	149 ± 27	138	146 ± 23
Baseline DBP, mmHg, mean±SD	706	82 ± 18	294	79 ± 14	137	80 ± 15
Site of occlusion	873		295		161	
Isolated MCA		469 (53.7)		208 (70.5)		102 (63.4)
ICA with or without tandem MCA		324 (37.1)		39 (13.2)		41 (25.5)
Vertebro-basilar		80 (9.2)		48 (16.3)		18 (11.2)

Previous use of IV thrombolysis	876	557 (63.6)	295	148 (50.2)	161	117 (72.7)
Onset to groin puncture, min, median (IQR)	848	210 (259-322)	295	167 (210-270)	157	160 (223-278)
Successful recanalization (TICI 2b/3)	840	663 (78.9)	294	182 (61.9)	161	116 (72.1)
All-cause mortality at 90-day	796	188 (23.6)	288	57 (19.8)	122	18 (14.8)
Favorable outcome (90-day mRs 0-2)	796	354 (44.5)	288	137 (47.6)	122	72 (59.0)
sICH	847	77 (9.1)	285	26 (9.1)	160	3 (1.9)

Values are number (percentage) unless otherwise as indicated.

Abbreviations: ASPECTS=Alberta Stroke Program Early CT score; DBP=diastolic blood pressure; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=middle cerebral artery; mRS=modified rankin scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure; SD=standard deviation; sICH=symptomatic intracerebral hemorrhage; TICI=thrombolysis in cerebral infarction.

Table S2. Patient's characteristics according to inclusion or not in primary analysis

	Primary analysis		Absolute
	Included (n=1042)	Not Included (n=290)	Standardized difference, %
Age, y mean ± SD	67.6± 15.0	66.0 ± 15.4	10.9
Men	538 (51.6)	162 (56.1)	8.9
Medical history			
Hypertension	587 (56.3)	154 (53.3)	6.1
Diabetes	163 (15.7)	52 (18.1)	6.6
Hypercholesterolemia	304 (29.2)	78 (27.2)	4.6
Current smoking	223 (22.8)	57 (19.9)	6.9
Antithrombotic therapy	399 (38.6)	103 (38.7)	0.4
Antiplatelet	*258 (24.9)*	*77 (29.0)*	*9.1*
Anticoagulant	*181 (17.5)*	*38 (14.3)*	*8.8*
NIHSS score, median (IQR)	16 (11-21)	16 (10-21)	1.7
DWI-ASPECTS, median (IQR)	7 (6-9)	8 (6-9)	1.9
Site of occlusion			
Isolated MCA	630 (60.5)	149 (51.6)	19.2
ICA with or without tandem MCA	307 (29.5)	98 (33.9)	
Vertrebo-basilar	105 (10.0)	42 (14.5)	
Previous use of IV thrombolysis	652 (62.6)	170 (58.6)	8.1
Onset to groin puncture, min, median (IQR)	242 (190-295)	264 (200-330)	21.4

Values are number (percentage) unless otherwise as indicated.

Abbreviations: ASPECTS=Alberta Stroke Program Early CT score; DBP=diastolic blood pressure; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure; SD=standard deviation.

Table S3. Patient's characteristics according to favorable outcome

	Favorable outcome (90-day mRs 0-2)		
	No (n=545)	**Yes (n=497)**	**P-Value**
Age, y mean ± SD	71.7 ± 13.9	63.2 ± 14.9	<0.001
Men	264 (48.4)	274 (55.1)	0.031
Medical history			
Hypertension	337 (61.8)	250 (50.3)	<0.001
Diabetes	111 (20.4)	52 (10.5)	<0.001
Hypercholesterolemia	165 (30.4)	139 (28.0)	0.39
Current smoking	101 (20.0)	122 (25.7)	0.034
Antithrombotic therapy	225 (41.5)	174 (35.3)	0.040
Antiplatelet	*140 (25.8)*	*118 (23.9)*	*0.48*
Anticoagulant	*112 (20.7)*	*69 (14.0)*	*0.005*
NIHSS score, median (IQR)	19 (14-22)	13 (8-18)	<0.001
DWI-ASPECTS, median (IQR)	7 (5-8)	8 (7-9)	<0.001
Baseline SBP, mmHg, mean±SD	152 ± 27	145 ± 24	<0.001
Baseline DBP, mmHg, mean±SD	82 ± 18	80 ± 15	0.15
Site of occlusion			
Isolated MCA	300 (55.1)	330 (66.4)	<0.001
ICA with or without tandem MCA	178 (32.7)	129 (26.0)	
Vertebo-basilar	67 (12.3)	38 (7.7)	
Previous use of IV thrombolysis	309 (56.7)	343 (69.0)	<0.001

Onset to groin puncture, min, median (IQR)	245 (195-305)	240 (186-288)	0.067
Successful recanalization (TICI 2b/3)	348 (64.6)	419 (85.3)	<0.001

Values are number (percentage) unless otherwise as indicated.

Abbreviations: ASPECTS=Alberta Stroke Program Early CT score; DBP=diastolic blood pressure; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure; SD=standard deviation.

Table S4. Patient's characteristics according to presence or absence of symptomatic intracerebral hemorrhage (sICH)

	sICH		
	No (n=925)	**Yes (n=98)**	**P-Value**
Age, y mean ± SD	67.5 ± 15.0	67.9 ± 14.3	0.80
Men	475 (51.4)	54 (55.1)	0.48
Medical history			
Hypertension	522 (56.4)	53 (54.1)	0.66
Diabetes	137 (14.8)	22 (22.5)	0.047
Hypercholesterolemia	272 (29.4)	29 (29.6)	0.97
Current smoking	195 (22.4)	24 (26.1)	0.42
Antithrombotic therapy	360 (39.2)	32 (33.0)	0.23
Antiplatelet	*234 (25.5)*	*21 (21.7)*	*0.41*
Anticoagulant	*161 (17.5)*	*16 (16.5)*	*0.80*
NIHSS score, median (IQR)	16 (11-20)	18 (14-22)	<0.001

DWI-ASPECTS, median (IQR)	7 (6-9)	6 (4-8)	<0.001
Baseline SBP, mmHg, mean±SD	149 ± 25	147 ± 26	0.47
Baseline DBP, mmHg, mean±SD	81 ± 17	81 ± 15	0.93
Site of occlusion			
Isolated MCA	582 (62.9)	42 (42.9)	<0.001
ICA with or without tandem MCA	255 (27.6)	43 (43.9)	
Vertebro-basilar	88 (9.5)	13 (13.3)	
Previous use of IV thrombolysis	581 (62.8)	59 (60.2)	0.61
Onset to groin puncture, min, median (IQR)	240 (193-295)	240 (180-290)	0.65

Values are number (percentage) unless otherwise as indicated.

Abbreviations: ASPECTS=Alberta Stroke Program Early CT score; DBP=diastolic blood pressure; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure; SD=standard deviation.

Table S5. Linear and polynomial logistic regression analysis of the association of favorable outcome with baseline systolic and diastolic blood pressure values

Blood Pressure	Model	β (95%CI)	P	Adjusted β (95%CI) *	P *	Adjusted β (95%CI)*†	P*†
Systolic	**Model 1**						
	Linear term	-0.1167 (-0.1663;-0.0671)	<0.001	-0.0565 (-0.0973;-0.0158)	0.007	-0.034 (-0.0854;0.0172)	0.19
		AIC=1424.25		AIC=1154.85			
	Model 2						
	Linear term	-0.1519 (-0.3151;0.6190)	0.52	0.4758 (-0.0413; 0.9930)	0.071	0.3807 (-0.1306; 0.8919)	0.14
	Quadratic term	-0.0087 (-0.0239;0.0064)	0.26	-0.0182 (-0.0348; -0.0016)	0.031	-0.0152 (-0.0315; 0.0011)	0.067
	Overall effect	*AIC=1424.92*	*<0.001‡*	*AIC=1148.87*	*0.003‡*		*0.002‡*
Diastolic	**Model 1**						
	Linear term	-0.0536 (-0.1274; 0.0203)	0.16	-0.0513 (-0.1134; 0.0109)	0.11	-0.0432 (-0.1257; 0.0392)	0.31
		AIC=1444.27		AIC=1159.50			
	Model 2						
	Linear term	0.4972 (-0.0157; 1.0102)	0.058	0.3124 (-0.2670; 0.8919)	0.29	0.2997 (-0.1967; 0.7961)	0.24
	Quadratic term	-0.0319 (-0.0617; -0.0021)	0.036	-0.0222 (-0.0557; 0.0113)	0.19	-0.0215 (-0.0500; 0.0070)	0.14
	Overall effect	*AIC=1440.96*	*0.025‡*	*AIC=1159.13*	*0.10‡*		*0.082‡*

β indicated regression coefficient associated with baseline BP (expressed per each increase in 10 mmHg) calculated from logistic regression models.

Model 1 indicated a linear logistic regression analysis and Model 2 indicated a non-linear (second order polynomial) logistic regression analysis. * logistic regression model stratified by center and adjusted for age, sex, history of hypertension and diabetes, baseline NIHSS, and prior use of thrombolysis.

†calculated after handling missing data on outcome, BP, and other covariates using multiple imputation procedure (m=10).

‡ overall BP effect calculated using a likelihood ratio test comparing the model with and without linear and quadratic BP terms.

Abbreviations: AIC= Akaike Information Criterion, BP=Blood pressure, CI=confidence intervals, NIHSS=National Institutes of Health Stroke Scale.

Table S6. Linear and polynomial logistic regression analysis of the association of symptomatic intracranial hemorrhage with baseline systolic and diastolic blood pressure values

Blood Pressure	Model	β (95%CI)	P	Adjusted β (95%CI) *	P *	Adjusted β (95%CI)*†	P*†
Systolic	**Model 1**						
	Linear term	-0.0310 (-0.1143; 0.0522)	0.46	-0.0218 (-0.1113; 0.0678)	0.63	-0.0232 (-0.1095; 0.0631)	0.60
		AIC=649.48		AIC=601.84			
	Model 2						
	Linear term	-0.0938 (-5.1875; 4.9999)	0.45	-0.3455 (-1.0638; 0.3728)	0.35	-0.2436 (-0.9327; 0.4455)	0.49
	Quadratic term	-0.2560 (-0.9173;0.4054)	0.50	0.0104 (-0.0124; 0.0332)	0.37	0.0071 (-0.0147; 0.0290)	0.52
	Overall effect	*AIC=651.06*	*0.62 ‡*	*AIC=1148.87*	*0.62‡*		*0.72‡*
Diastolic	**Model 1**						
	Linear term	0.0058 (-3.3312; -1.2524)	0.93	0.0086 (-0.1211; 0.1383)	0.90	0.0051 (-0.1216; 0.1317)	0.94
		AIC=650.01		AIC=602.05			
	Model 2						
	Linear term	0.3922 (-7.7480; -0.0658)	0.39	0.3701 (-0.5217; 1.2618)	0.42	0.2536 (-0.5795; 1.0867)	0.55
	Quadratic term	-0.0222 (-0.5069; 1.2913)	0.40	-0.0208 (-0.0724; 0.0307)	0.43	-0.0134 (-0.0582; 0.0314)	0.56
	Overall effect	*AIC=651.15*	*0.65‡*	*AIC=603.29*	*0.68‡*		*0.84‡*

β indicated regression coefficient associated with baseline BP (expressed per each increase in 10 mmHg) calculated from logistic regression models.

Model 1 indicated a linear logistic regression analysis and Model 2 indicated a non-linear (second order polynomial) logistic regression analysis. * logistic regression model stratified by center and adjusted for age, sex, history of hypertension and diabetes, baseline NIHSS, and prior use of thrombolysis.

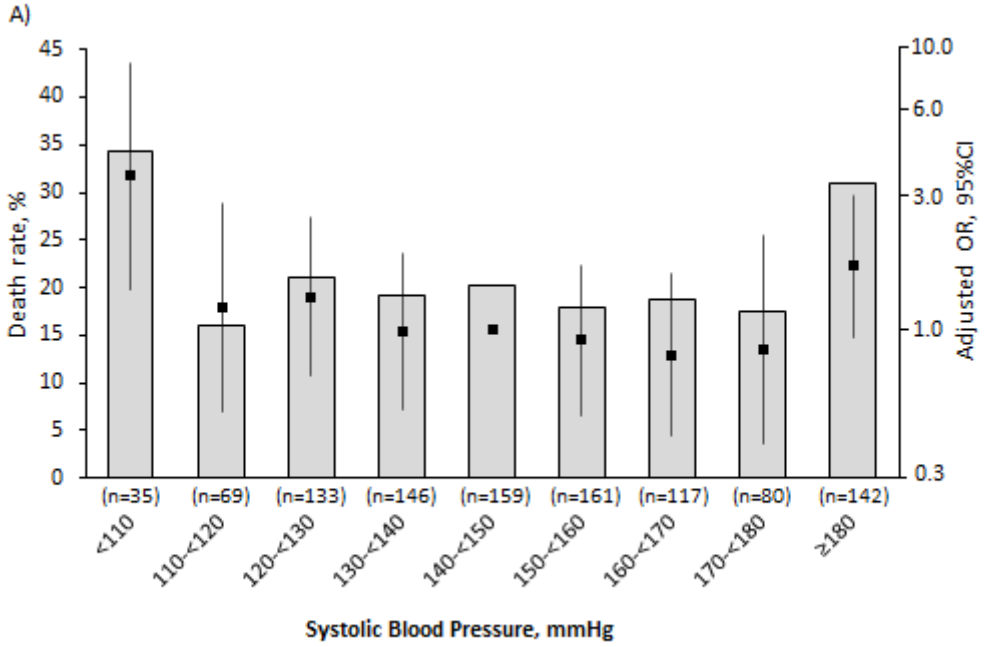
†calculated after handling missing data on outcome, BP, and other covariates using multiple imputation procedure (m=10).

‡ overall BP effect calculated using a likelihood ratio test comparing the model with and without linear and quadratic BP terms.

Abbreviations: AIC= Akaike Information Criterion, BP=Blood pressure, CI=confidence intervals, NIHSS=National Institutes of Health Stroke Scale.

Supplemental Figures

Figure S1. Incidence and adjusted Odds ratio of 90-day all-cause mortality as function of baseline systolic (A) and diastolic (B) blood pressure categories. Adjusted odds ratio were calculated in logistic regression models stratified by center and adjusted for age, sex, history of hypertension and diabetes, baseline NIHSS, and prior use of thrombolysis by medium BP category as reference.



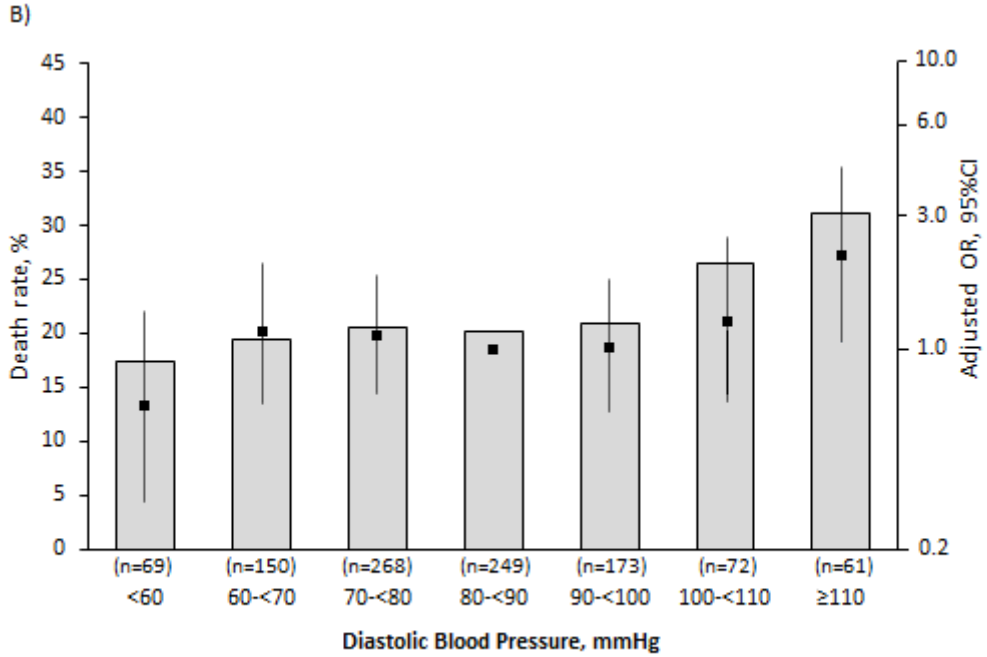
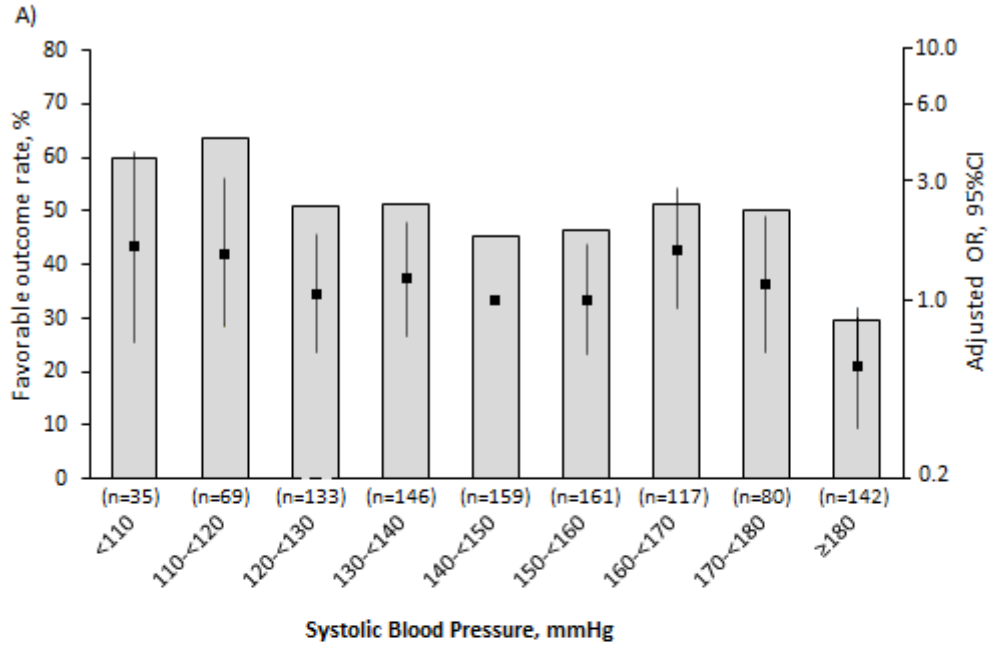


Figure S2. Incidence and adjusted Odds ratio of 90-day favorable outcome as function of baseline systolic (A) and diastolic (B) blood pressure categories. Adjusted odds ratio were calculated in logistic regression models stratified by center and adjusted for age, sex, history of hypertension and diabetes, baseline NIHSS, and prior use of thrombolysis by using the medium BP category as reference.



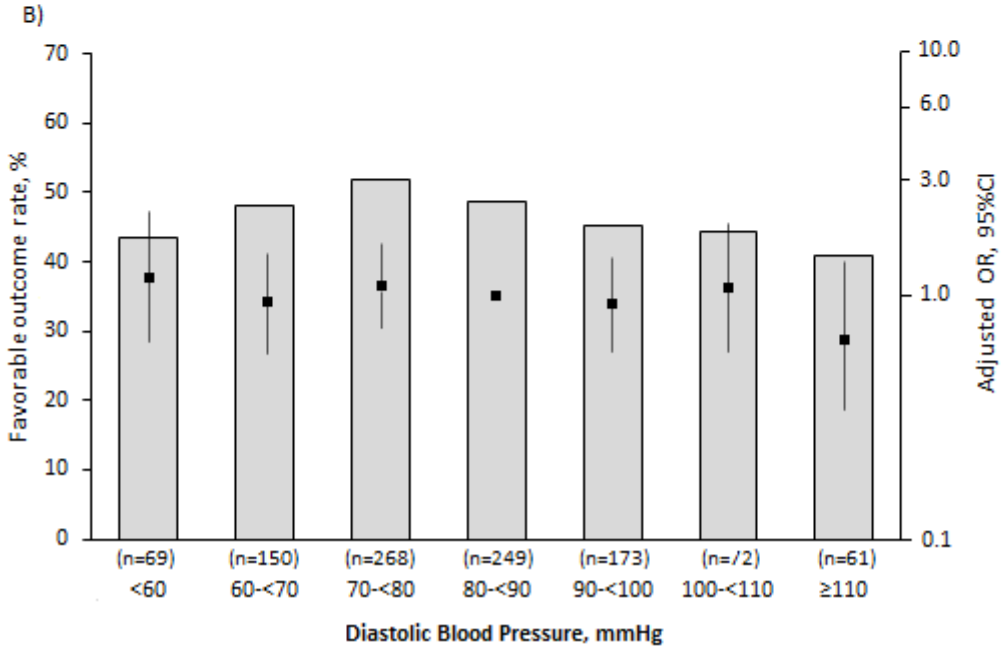


Figure S3. Incidence and adjusted Odds ratio of symptomatic intracerebral hemorrhage (sICH) as function of baseline systolic (A) and diastolic (B) blood pressure categories. Adjusted odds ratio were calculated in logistic regression models stratified by center and adjusted for age, sex, history of hypertension and diabetes, baseline NIHSS, and prior use of thrombolysis by using the medium BP category as reference.